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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,528	01/29/2004	Karl Salzwedel	1900.0430002/LBB/SJE	2237

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,528	SALZWEDEL ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,12,13 and 82-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,12,13 and 82-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Arguments

This Office Action is in response to the amendment filed 22 January 2007. Claims 8, 11, and 14-81 have been cancelled. Claims 1-7, 9, 10, 12, 13, and 82-84 are pending.

Double Patenting

The Examiner appreciates the Applicants for pointing out the typographical error in the copending Application no. in the previous Office Action on 21 September 2006. The Examiner apologizes for the oversight.

The provisional nonstatutory double patenting rejection of claims 1-10, 12, 13, and 82-84 as being unpatentable over claims 1-10, 19, 21, 22, and 24-25 of copending Application No. 10/851,637 is withdrawn in view of Applicants' cancellation of the conflicting claims in Application no. 10/851,637.

Claim Rejections - 35 U.S.C. §112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-10, 12, 13, and 82-84 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **maintained**.

Examiner's rejection in the Action mailed on 21 September 2006 is as follows:

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed

invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

M.P.E.P. § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." M.P.E.P. § 2163 also states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See M.P.E.P. § 2163. Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are directed to a method of treating HIV-1 infection in a patient, comprising administering to a patient a compound that selectively inhibits processing of the viral Gag p25 protein (CA-SP1) to p24 (CA). The scope of the invention encompasses all compounds and functional derivatives or homologs that inhibit processing of viral Gag p25. Thus, the claims are drawn to a genus of compounds that is defined only by a functional characteristic.

The specification only provides description for one compound, 3-O-(3',3'-dimethylsuccinyl) betulinic acid (DSB). See spec. ¶26, and examples. There is no disclosed correlation between function and structure beyond the DSB disclosed in the examples in the specification. Neither does the specification identify any partial structure that must be conserved for inhibition of viral Gag p25 processing. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus.

Applicant argues that: (1) Applicants provided a number of compounds that function as maturation inhibitors, and detailed information about the compound's substrate, Applicants have also provided detailed procedures for testing a compound to determine its suitability as a maturation inhibitor at least in paragraphs 109-112; (2) the application's specific content is buttressed by the documents incorporated by reference in the application as originally filed.

Applicant's arguments have been fully considered but are not persuasive. The limitation, "a compound that selectively inhibits processing the viral Gag 25 protein (CA-SP1) to p25 (CA)," in the instant claims encompass a broad genus of inhibitor compounds including siRNA, aptamers, ribozymes, antibodies, small molecule compounds, peptidomimetics, and any homologs of Gag-binding proteins. The present specification only provides structural guidance to one chemical compound, 3-O-(3',3'-dimethylsuccinyl) betulinic acid (DSB) (¶ 26). Applicants' reference to the procedures for identifying suitable maturation inhibitors in the specification ¶ 109-112 does not address the written description issue because the disclosure is no more than Applicants' desire to obtain new inhibitors. This does not allow one skilled in the art to envision the chemical structure of the compound that is critical for the claimed inhibition activity.

The disclosure as incorporated by reference does not describe any of the other small molecule inhibitors as well as the other subgenus compounds such as siRNA, aptamers, ribozymes, antibodies, peptidomimetics, and any homologs of Gag-binding proteins. The specification and the incorporated references describe 3-O-(3',3'-dimethylsuccinyl) betulinic acid (DSB), oleanolic acid, promolic acid, and platanic acid, which are not sufficient to represent the aforementioned compounds.

Neither the specification nor the incorporated references describe the critical structure required for the intended inhibition activity. The few disclosed chemical compounds do not reflect the inordinate number of species that are neither described or contemplated by the Applicants. Therefore, Applicants have not presented any

objective evidence to show that Applicants were in possession of entire genus encompassed by the invention at the time of filing the application.

The rejection of claims 1-10, 12, 13 and 82-84 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is **maintained**.

Examiner's rejection in the Action mailed on 21 September 2006 is as follows:

The nature of the invention is a method of treating HIV-1 infection in a patient, comprising administering to a patient in need thereof a compound that selectively inhibits processing of the Viral Gag p25 protein (CA-SP1) to p24 (CA). At the time the invention was made, successful implementation of HIV/AIDS therapy with a Gag p25 inhibitor was not routinely obtainable by those skilled in the art. The broad claims encompass treatment of all clades and subtypes of HIV in a patient. The working examples disclose *in vitro* inhibition of HIV infection in HeLa cells. The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to a cell culture assay to determine the inhibitory effect of DSB on HIV maturation (spec. pages 53-54, Example 3, ¶159). There is no evidence that shows any correlation with *in vivo* efficacy. There is not even a test to determine the cytopathic effect and resistance of the claimed genus of Gag p25 inhibitors. *In vitro* testing is, at most, useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment due to the high level of unpredictability of this art.

The state of the art of development of pharmaceutical HIV inhibitors is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the Darwinian selective pressures. Therefore, efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations. Besides the problem of rapid emergence of drug-resistance HIV variants, the disclosed *in vitro* test is unreliable in detecting the drug susceptibility of minority HIV-1 variants in the virus population because resistant mutants may not persist at detectable levels in the absence of drug selection pressure (Martinez-Picado, 1998, pages 84, 85, and 87), which increases the complexity in extrapolating from *in vitro* to *in vivo* test results. For determining *in vivo* efficacy, one skilled in the art has to address many factors such as serum half-life, bioavailability, clearance of the drugs themselves (Gait, 1995, page 437), cellular uptake, transport, metabolic activation, cell-, tissue-, and organ-specific toxicity (Lee, 2003, page 14713), all of which affect the concentration of the active form of the drugs at the site of action. Due to the highly unpredictable nature

of HIV-infection, extrapolating from *in vitro* models to whole organisms without *in vivo* validation is hazardous and unpredictable.

Absent working examples and specific teachings of the efficacy in humans, therapeutic index, and pharmacokinetic -properties of the Gag p25 inhibitors, those in the art would not be able to use the claimed method for the treatment of HIV infection. One skilled in the art is burden with the undue experimentation of clinical efficacy, therapeutic index, and pharmacokinetic properties of the genus of Gag p25 inhibitors because one can use the claimed method. Applicants have identified a candidate compound, DSB, that affects HIV maturation, but essentially all of the work required to ultimately develop a treatment method has been left for others.

Applicant argues that: (1) a plurality of maturation inhibitors were obtainable by those skilled in the art and the state of art for anti-retroviral therapy was quite advanced; (2) Applicants assert that the disclosure of 5 cell types infected with either wild type or 1 of 7 drug resistant mutant viruses constitutes a broad range of working examples; (3) the highly conserved genetic sequence of Gag and the claim element limiting treatment to HIV-1 (rather than all viral Gag proteins) make the correlation of *in vitro* and *in vivo* results even stronger; (4) the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example and a rigorous or an invariable exact correlation is not required; (5) As the present application provides considerable guidance respecting active compounds, substrate identity, and detailed testing procedures.

Applicant's arguments have been fully considered but are not persuasive. Applicants seem to have misconstrued the examiner's analysis of the *Wands* factors. (1) The state of prior art does not provide routine practice of the claimed method of treating HIV-1 infection in a patient with a compound that selectively inhibits processing of the viral Gag p25 protein to p24. The teachings of a maturation inhibitor and anti-

retorviral therapy using other inhibitors are not analogous to the claimed treatment in a patient. (2) The working examples of cell assays do not support the full breadth of the claimed invention due to the lack of correlation between *in vitro* HIV inhibition results and therapeutic treatment in a patient. (3) Applicants' assertion that the highly conserved Gag sequence and limiting the treatment to HIV-1 make the correlation of *in vitro* and *in vivo* results even stronger does not have evidentiary basis. As set forth previously, the disclosed *in vitro* test is unreliable in detecting the drug susceptibility of minority HIV-1 variants in the virus population because resistant mutants may not persist at detectable levels in the absence of drug selection pressure. The tested mutants (Table 4) were developed under selective pressure of reverse transcriptase inhibitors and hence are not predictive of the mutants that will arise in the patients under the selective pressure of the claimed maturation inhibitors. (4) The examiner's reason for the conclusion of lack of correlation for an *in vitro* has already been set forth in the previous Action and reiterated above. (5) The disclosure of active compounds, substrate identity, and detailed testing procedures is merely an invitation to further undue experimentation to identify the putative compounds that might function in the desired manner. The disclosure fails to provide sufficient guidance pertaining to the structural characteristics of those compounds that are capable of inhibiting HIV-1 Gag processing to p24 in a selective manner. The disclosure is silent pertaining to the identification of a common inhibitor motif in the compound of interest. The disclosure is silent regarding the pharmacological efficacy of the claimed genus of inhibitors.

More importantly, Applicants' arguments are insufficient to address the high level of unpredictability in the art, which is the reason for the lack of correlation between *in vitro* cell assay and patient treatment. The present specification does not describe any therapeutic property such as the binding specificity, selectivity and affinity, oral bioavailability, plasma concentration, cellular uptake, toxicity, lethal dose, or side effects of the broad genus of maturation inhibitors. One skilled in the art would not be able to treat a patient without such guidance. It has been well known in the prior art (Gait, 1995) that the development of suitable HIV-1 therapeutics has been an arduous and empirical process, often ending in failure. This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of in vitro tissue culture studies and in vivo animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable in vitro and in vivo activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved,

new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage. Therefore, it requires undue and unpredictable experimentation to validate the efficacy of the genus of maturation inhibitors and to determine how to use the claimed method.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
01 April 2007

Louise Humphrey, Ph.D.
Assistant Examiner